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Current Situation and Challenges in Vitreous Substitutes

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Vitreo-retinal disorders constitute a significant portion of treatable ocular diseases. These pathologies often require vitreo-retinal surgery and, as a consequence, the use of vitreous substitutes. Nowadays, the vitreous substitutes that are used in clinical practice are mainly divided into gases (air, SF_6, C_2F_6, C_3F_8) and liquids (perfluorocarbon liquids, silicone oils, and heavy silicone oils). There are specific advantages and drawbacks to each of these, which determine their clinical indications. However, developing the ideal biomaterial for vitreous substitution continues to be one of the most important challenges in ophthalmology, and a multidisciplinary approach is required. In this sense, recent research has focused on the development of biocompatible, biodegradable, and injectable hydrogels (natural, synthetic, and smart), which also act as medium and long-term internal tamponade agents. This comprehensive review aims to cover the main characteristics and indications for use of the extensive range of vitreous substitutes that are currently used in clinical practice, before going on to describe the hydrogels that have been developed recently and which have emerged as promising biomaterials for vitreous substitution.

1. Introduction

The vitreous humour is a transparent gel present between the lens and the retina. It has a volume of around 4 mL and occupies 80% of the eye volume.[1,2] It weighs around 4 g and contains approximately 99% water, only adhering to ocular structures in the following parts: the macula, the optic nerve disc, and the anterior border of the area surrounding the retina.[2]

Vitreo-retinal disorders constitute a significant portion of treatable ocular diseases. The vitreous humour often becomes dysfunctional due to opacification, liquefaction or physical collapse, as a result of inflammatory diseases, developmental abnormalities, vitreous hemorrhage, tumors, diabetes, or degenerative processes. In addition, vitreous damage can also be caused by intraocular foreign bodies or trauma.[3] The vitreous humour determines the clarity of vision meaning

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therefore that, if not treated properly, these disorders can cause blindness. Vitreous substitutes are crucial adjuncts during vitreo-retinal (VR) surgery for retinal diseases.[2,4,5]

Nowadays, the most common agents that are used as vitreous substitutes in clinical practice boast certain advantages, including chemical inertness and optical clarity, nonetheless, there are also many limitations to their use.[2] In this sense, the development and characterization of new vitreous substitutes have played an important role in vitreo-retinal surgery. Despite the fact that considerable efforts have been made in developing new biomaterials for vitreous substitution in search of the perfect alternative that is able to overcome the disadvantages presented by the currently available substances, further research must be performed. In this regard, developing the ideal biomaterial for vitreous substitution continues to be one of the most significant challenges in ophthalmology. Given the complexity of this matter, a multidisciplinary approach, which involves ophthalmic surgeons, pharmacists, chemists, and experts in biomaterials will be necessary if we want to overcome this problem.

Our aim is to discuss the main characteristics and applications of the wide variety of vitreous substitutes that are currently used in clinical practice, before going on to address the development of new hydrogels that have been presented as promising alternatives for the optimization of vitreous substitution.

2. Composition and Functions of the Vitreous

The vitreous is a gelatinous structure that is composed of 98% water.[3,4] It protects the adjacent structures and tissues from traumas, as well as permitting the circulation of nutrients and solutes, and controlling the oxygen tension within the eye. It helps to maintain the shape of the ocular globe, as well as keeping the crystalline lens and the retina in their place.[3,6] The main components of the vitreous humour, as well as the major characteristics of the aforementioned components are outlined below.

2.1. Proteins

Proteins represent a small percentage of the overall content of the vitreous components. The majority of the soluble proteins are albumin (40%), with the other important components including immunoglobulins and iron-binding proteins such as transferrin, which helps to reduce iron toxicity in the case of small hemorrhages.[1,6,7] With regards to insoluble proteins, collagens are the most abundant. There are different types of proteins which play a major role in the vitreous structure.[4,8]

2.2. Glycosaminoglycans (GAGs)

GAGs, which are extracellular polysaccharides are a key component of the vitreous structure, and these are mainly divided into three types—hyaluronic acid, heparan sulfate, and chondroitin sulfate.[1]

2.2.1. Hyaluronic Acid (HA)

HA is a major component of the vitreous, forming 3D structures with collagen. The fact that it does not contain sulfate makes it distinguishable from the other GAGs, and this also means that it does not attach to proteins to form a proteoglycan.[1] The highest concentrations of hyaluronan molecules are found in the posterior vitreous cortex.[6,9–11] The HA preparations consist of molecules with greater variability in terms of hydrodynamic size, and these are a relevant component in determining vitreous viscosity.[12]

2.2.2. Chondroitin Sulfate (CS)

CS is a sulfated GAG, which consists of a chain of alternating sugars (*N*-acetylgalactosamine and glucuronic acid). It constitutes a major component of the extracellular matrix and is also present in the vitreous, appearing in the form of the proteoglycans versican and type IX collagen.[4,11] CS is used to preserve the integrity of the vitreous and provide resistance against compression.[1]

2.2.3. Heparan Sulfate (HS)

HS is a renewable proteoglycan, which ensures that there is adequate spacing between the collagen fibrils, nonetheless, small amounts of HS are present in the vitreous.[13] It also enhances the regulation of angiogenesis and blood coagulation, as well as maintaining vitreo-retinal adhesion.[4]

2.3. Glucose, Lactic Acid, and Antioxidants

Due to the important role that the vitreous plays in the cellular metabolism of ocular tissues, its components include several substances that act as subtracts for metabolism, such as glucose and lactic acid, which are necessary to support the metabolism in the surrounding tissues.[4,6] In addition, the vitreous acts as a reservoir of glucose for the ciliary body.[14]

On the other hand, ascorbic acid is a crucial antioxidant for lens and retinal metabolism, in particular it is used as a metabolic buffer in potassium homeostasis. Furthermore, it may also inhibit neovascularization and increase the proliferation of hyalocytes.[15–17]

2.4. Cells and Enzymes

There are three types of cells that are found in the vitreous body: hyalocytes, fibrocytes/fibroblasts, and macrophages.[6,18,19] The main functions of these cells are related to the creation, regulation, and degradation of the vitreous matrix. Several enzymes have been isolated, which include hyaluronidase, serine proteases, and renin-angiotensin-converting enzyme.[20–22]

3. Vitreous Substitutes in Clinical Practice

Vitreous substitutes must have physical and biological properties that make them suitable for use in clinical practice. In terms of their physical properties, ideal vitreous substitutes will be hydrophilic and insoluble in water, easy to manipulate during surgery, clear and transparent to facilitate visualization, and

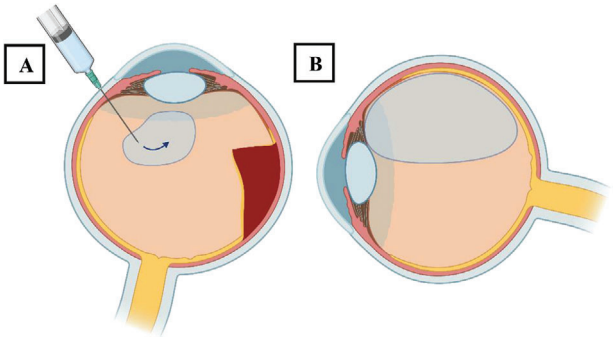

Figure 1. Gas injection in pneummoretinopexy. A) Example of a superior detachment and injection with the patient lying in the supine position (face-up). B) The patient is placed in an upright position and the bubble tamponades the break. Created with BioRender.com.

they will also have a refractive index that is similar to the human vitreous. In addition, these must remain stable when injected through a small syringe, as well as ensuring adequate surface tension in the attempt to seal the retinal break.[2,23] On the other hand, and in terms of their biological properties, the ideal vitreous substitutes will be biodegradable and biocompatible, biologically and chemically inert, and they will not block the aqueous drainage. Furthermore, they must be nontoxic to retinal tissues.[6,23]

An ideal vitreous substitute does not yet exist; all of them offer advantages and drawbacks, which may or may not make them suitable depending on the clinical situation. Those currently used in clinical practice are divided into different categories based on different properties. Specifically, these are divided into gases (air, SF_6, C_3F_8, and C_2F_6) and liquids (salt solution, silicon oils (SO), perfluorocarbon liquids, and semi fluorinated alkanes). The characteristics of each individual group, as well as their clinical indications have been outlined in detail in the following sections.

3.1. Gases

Ohm was the first to describe intraocular gas use in 1911.[24] Several indications for its use were described, with the first of these being its use as an internal tamponade.[25] It also proves useful in unfolding and folding the retina, as well as in improving its postoperative visualization and replacing the globe volume to prevent fluid movement into retinal breaks. Gas is also used in several techniques: pneummoretinopexy (**Figure 1**); the pars plana vitrectomy for retinal detachment (RD), with and without scleral buckle, to flatten the retina; subretinal blood displacement in macular hemorrhages; and postvitrectomy liquid–gas exchange in previously vitrectomized eyes.[26]

Postoperative care is very important in these patients. Prone (face-down) positioning must commence as soon as possible after the vitrectomy procedure has been performed. This is crucial in preventing any shift of the reattached retina. Moreover, it decreases the contact between the posterior surface of the lens with the gas bubble in phakic patients (the bubble is situated towards the retina); therefore, reducing the risk of cataract formation. Positioning may also vary depending on the location of the retinal break, usually lying on the opposite side of the break.

The most widely used intraocular gases are sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8). These are nontoxic and inert gases that are insoluble in the aqueous humour, and they boast a lower water solubility than nitrogen therefore allowing them to expand.[27] The decision as to which one of these gases is to be used will be based on the tamponade duration and the surgeon's preferences, taking into consideration the type and location of the retinal break.[28]

It is generally accepted that SF_6 can be used in uncomplicated primary RD. However, if a final tamponade action is necessary, based on the results from "The Silicone Study", in which the results in patients with RD and proliferative vitreoretinopathy (PVR), the pars plana vitrectomy with either C_3F_8 gas or SO tamponades were favorable.[29] However, the clear advantage of using gases is that it is not necessary to remove them.

There are three stages in the absorption of the intraocular gas: expansion of the gas when injected, nitrogen equilibrium, and dissolution.[30] Gases may be absorbed by diffusion across the retina into the blood stream, or they may be dissolved into the aqueous humour, and removed through the anterior chamber.[31] The absorption of these gases demonstrates first-order pharmacokinetics, with small volumes lasting in the intraocular cavity for days or weeks depending on the gas used.[30]

Knowledge of the kinetics of these gases, as detailed in **Table 1**, comes mostly from animal models and small studies in which indirect measurements have been taken in humans.[30–35] These studies may not be representative of current practice, especially with regards to the duration of the air bubble in the posterior chamber of the eye, which is perceived to be longer in clinical settings than in theoretical ones.[36,37] The half-life of intraocular gases is shorter in aphakic eyes than in phakic eyes, due to the increased convection in the vitreous cavity.[38] Following the vitrectomy procedure, convection currents appear in the aphakic eye, which accelerate the absorption rate. In phakic eyes with normal vitreous, there are much fewer convection currents; therefore, the expansion and absorption of long-acting gases is slower.[30]

3.1.1. Air

Room air tamponade applied using non-expansible gas begins to shrink immediately after injection as it dissolves in the vitreous.[28] This offers an advantage over other long-lasting gases as it requires shorter prone positioning, allowing for a faster recovery of vision and less adverse effects.[41]

The half-life of a room air tamponade was 1.6 d in phakic eyes[30] with a longevity of 5 d, but recent clinical impressions have suggested that air remains in the vitreous cavity for a longer period of time. In a recent retrospective cohort study, a half-life of 3.3 d with a longevity of 11.4 d was determined.[37]

3.1.2. Other Gases: SF_6, C_2F_6, C_3F_8

Sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8) are the most commonly used intraocular gases in clinical practice, compared to hexafluoroethane (C_2F_6) which is much less frequently used.[36]

Table 1. Pharmacokinetics of intraocular gases.

Gases	Nonexpansile concentration	Duration of maximal expanded volume [h]		Half-life [d]		Duration of air bubble [d]		Indications
		Rabbits	Humans	Rabbits	Humans	Animals	Humans	
Air	–	Nonexpansible		–	1.6[a] 0.9[b]	5–6	10.7–11.4[c]	- Simple cases in which a short duration is required
SF_6 (sulfuric hexafluoride)	20%	24–48	21	–	2.6[a] 2.4[b]	8–11	18[a),c)]	- RD (Retinal detachment) with superior breaks - RD with inferior breaks - Flat RD in the case of meticulous vitreous dissection. - Following macular hole surgery
C_2F_6 (hexafluoroethane)	16%	72	27	2	–	16	34.5[a),c)]	Not approved by FDA
C_3F_8 (perfluoropropane)	12%	72–96	30	6	5.7[a] 4.5[b] 4.3[c]	28	67.7[a),c)]	- RD and multiple breaks - RD with superior giant tear - RD with proliferative vitreoretinopathy (PVR) - Failed prior RD surgery - Persistent subretinal fluid - Following macular hole surgery - Pneumatic displacement of subretinal blood clot
Ref.	[28]	[33,39]	[36]	[31]	[30]	[32,34]	[36,37,40]	[25]

[a] Referring to phakic eyes; [b] Referring to aphakic eyes; [c] Referring to pseudo-phakic eyes.

Given that these gases boast a lower water solubility than nitrogen, they tend to expand to at least twice the volume of the gas injected, as a result, nonexpansile or minimally expansile mixture of gas is preferable in order to prevent adverse effects such as intraocular pressure elevation (IOP).[28]

Water solubility varies depending on the carbon chain length. The longer the carbon chain, the lower the solubility in water; therefore, resulting in a longer intraocular longevity:[42] A mixture of 10% C_3F_8 had a half-life of 5.7 d in phakic and 4.3 d in pseudophakic eyes.[30] A mixture of 20% SF_6 had a half-life of 2.8 d in phakic eyes. The half-life of C_2F_6 was not measured; however, a longevity of 34 d was determined in the vitreous cavity.[36]

Certain postoperative complications have been reported following the use of intraocular gas, however, most of these can be prevented by taking greater care when undertaking the surgical procedure. For example, gas could go under the retina although this is preventable, or gas could become entrapped at the injection site.

One of the most frequent complications is the formation of cataracts due to the gas coming into contact with the crystalline lens.[43] Raised intraocular pressure may occur, but this tends to happen on the first postoperative day, and its cause has been attributed to the expansion of the bubble or to an overfilled eye. On the contrary, hypotony may occur if there is any gas leakage from the sclerotomies. Other complications include the presence of gas in the anterior chamber, secondary corneal decompensation,[44] which is more frequent in aphakic patients, and non-intact posterior capsule. In pseudophakic patients, intraocular lens capture may occur due to it being pushed forward into the anterior chamber.[45,46]

3.2. Liquids

Different liquid vitreous substitutes are used in clinical practice. The main groups and their major characteristics are depicted in **Table 2**.

3.2.1. Salt Solutions

Salt solutions have similar characteristics to aqueous humour in terms of their density, refractive index and transparency.[3] In the clinical setting, these are used on a temporary basis during the exchange with air or liquids as their low surface tension means that these do not have tamponade properties.[4]

3.2.2. Silicon Oil

Silicon oil (SO) is a polymerized siloxane with organic side chains. It belongs to the class of synthetic organosilicon compounds and is a repetition of the $-[R_2Si-O]-$ group in which R is the organic side chain.[47] Specifically, SOs used as vitreous substitutes are polymers of polydimethylsiloxane (PDMS).

In contrast to silicone rubber, polymer chains are shorter, and given the lack of chemical cross-linking between them, these present in a liquid form. They are hydrophobic substances with a specific gravity, which is slightly lower than water, and a refractive index that is higher than that of the vitreous.[48] These are available in different viscosities, which is measured in centistokes (cSt), and which ranges from 1000 to 5000 cSt in clinical practice.

Table 2. Physical properties of liquid vitreous substitutes and clinical indications.

Product	Specific gravity [g cm^{-3}]	Viscosity [cSt]	Refractive index	Indications
A. SALT SOLUTIONS				
BSS	1			Temporary replacement during air/oil exchange
B. SILICON OILS				
SO 1000 cSt	0.97	1000	1.4	Complex RD associated with PVR
SO 2000 cSt	0.97	2000	1.4	Giant tear, RD with PVR Traumatic RD with PVR Recurrent RD with breaks involving the lower quadrants RD associated with severe proliferative diabetic retinopathy
SO 5000 cSt	0.97	5000	1.4	RD associated with macular hole in pathologic myopia Pediatric RD RD associated with viral retinitis Posttraumatic endophthalmitis
C. PERFLUOROCARBON LIQUIDS				
Perfluorooctane (C_8F_{18})	1.76	0.69	1.27	Primary Rhegmatogenous RD
Perfluorodecalin ($C_{10}F_{18}$)	1.94	2.7	1.33	Complicated RD with PVR
Perfluoroperhydrophenanthrene ($C_{14}F_{24}$)	2.03	8.03	1.31	Giant tear RD with PVR
Octafluoropropane (C_3F_8)	1.6	0.465	1.22	RD associated with disc coloboma, Dislocated lens, Suprachoroidal hemorrhage
iv.SEMIFLUORINATED ALKANES				
Perfluorohexyloctane (F_6H_8)	1.35	3.44	1.387	
D. SFA-SO combinations				
(a) Double fillings				
(b) Heavy Silicon Oils				
Densiron-68	1.06	1387	1.39	RD associated with inferior tears and PVR
Oxane HD	1.02	3300	1.4	
HWS 46–3000	1.12	2903	1.37	

Since the 1960s, SO have been used as short and long-term vitreous substitutes because of their transparency, low surface tension, buoyancy, and low toxicity. The role of SO in clinical practice was defined by "The Silicone Study",[49,50] a multicentre prospective randomized clinical trial that compared the effect of SO to long-acting intraocular gases (SF_6 and C_3F_8) in the management of complex RDs associated with severe PVR. Globally, SO was demonstrated to be more effective than SF_6, and equally as effective as C_3F_8 in reattaching the retina.[49] In addition, SO and C_3F_8 produced very similar results in terms of the improvement of visual function and the low complication rates. Furthermore, the ophthalmologist's preference or the need for the patient to take a flight soon after the intervention could be reasons for using SO.[1]

The use of SO in giant tears without PVR is still being debated. In this sense, good anatomic success has been reported with SO and gases. Generally speaking, SO is the most used agent in Europe, while in the United States some ophthalmologists still have a preference for intraocular gas.[51]

SO tamponade tends to be administered at the primary vitrectomy for traction RD associated with severe proliferative diabetic retinopathy.[52] However, to date, no clinical trials have adequately evaluated its efficacy in this use. In addition, with regards to the treatment of RDs in viral retinitis, SO offers long-term internal tamponade, therefore decreasing the risk of re-detachment.[53,54]

Regarding the pediatric population, the main indications for the use of SO tamponade are RDs associated with retinopathy of prematurity, trauma, congenital anomaly, and myopia. In the case of severe traumatisms, SO internal tamponade may help to flatten the retina and prevent hemorrhage, which would increase the risk of PVR.[55]

Finally, it has been argued that SOs have certain antimicrobial activity, which is why they are usually used as a tamponade in posttraumatic endophthalmitis cases.[56]

With regards to the disadvantages of SOs, these include the need for optical adjustments to be made due to the different refractive index when compared to the natural vitreous body, and the less effective nature of the use of the tamponade in treating inferior retina breaks due to its low specific gravity.[57,58]

Furthermore, serious complications such as retinal toxicity,[59] optical neuropathy,[60] or glaucoma [61] have been reported with the use of SO, some of which are related to the emulsification of SO, especially in long-term use. This emulsification leads the original SO bubble to break down into smaller droplets, resulting in retinal inflammation by inducing a macrophagic response.[62]

SOs must be removed as soon as they have fulfilled their purpose, and when it is established that further retention could increase the risk of complications (**Figure 2**). This removal is generally recommended within a six-month period after the intervention.

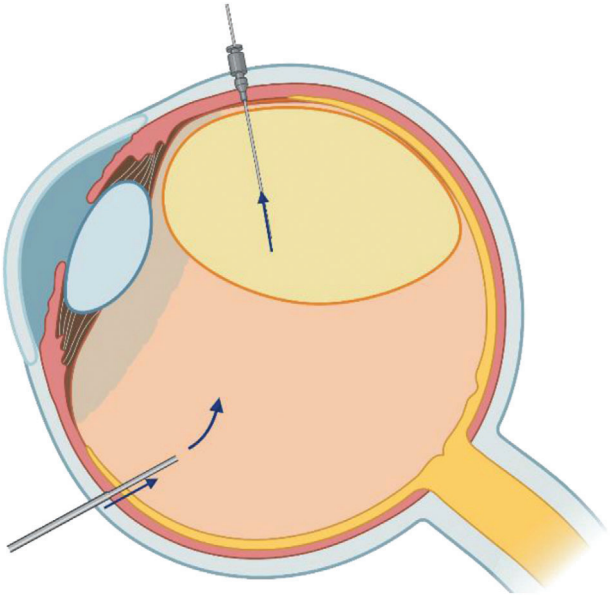

Figure 2. Silicone oil (SO) removal through active suction with machine assistance. Created with BioRender.com.

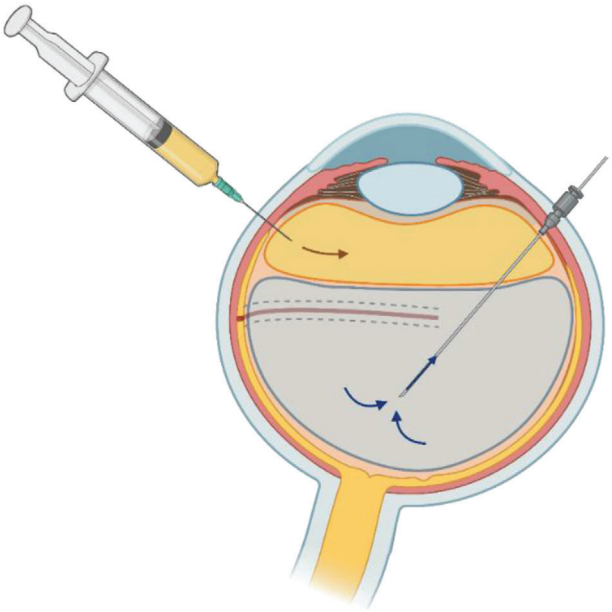

Figure 3. Perfluorocarbon liquid (PFCL) – silicone oil (SO) exchange. SO is filled progressively superiorly, while PFCL is extruded through the flute needle placed within the PFCL bubble. Created with BioRender.com.

3.2.3. Perfluorocarbon Liquids

Perfluorocarbon liquids (PFCLs) are fluorine-substituted hydrocarbons, which are clear, colorless and odorless liquids. These synthetic compounds are characterized by a high specific gravity, between 1.7 and 2.1 g cm^{-3}, twice as high as water, and their refractive index is similar to that of the vitreous humour.[63] They are insoluble in water and poorly soluble in SOs. The most commonly used PFCLs in clinical practice are perfluorodecalin ($C_{10}F_{18}$), perfluoroperhydrophenanthrene ($C_{14}F_{24}$), perfluorooctane (C_8F_{18} and octafluoropropane (C_3F_8).[4] Historically, these were first investigated as blood substitutes due to their extensive capacity for transporting and releasing oxygen and carbon dioxide.[64]

In the clinical setting, the use of PFCLs has improved the visual outcomes and the anatomic success rate in PVR surgical procedures.[65–68] PFCLs provide the best currently available internal tamponade during membrane dissection. Similarly, the use of PFCLs in treating giant-tear RD has improved the anatomic success rate by over 90%.[66] The PFCLs allow for the repositioning of the folded flap, enabling direct PFCL-SO exchange in order to prevent the posterior flap from slipping.

PFCLs also offer several advantages in the treatment of traumatic RD, including the stabilization of the retina during the vitrectomy procedure, the displacement of preretinal, subretinal, and suprachoroidal blood, the elimination of incarcerated vitreous or retina, and the maintenance of a transparent medium for visualization during surgery.[69]

The use of PFCLs in other ophthalmic pathologies has already been proved, for example in cases of RD associated with diabetic retinopathy,[70] detachment associated with disc coloboma,[71] detachment from retinopathy of prematurity,[72] vitrectomy for endophthalmitis, displacement of submacular hemorrhage during surgical drainage, and the excision of subretinal membranes.[73]

With regards to the safety of PFCLs, in recent years, several cases of retinotoxicity caused by perfluorooctane have been reported worldwide. In this regard, it is necessary for strict protocols to be established to determine the cytotoxicity of intraocular medical devices in order to ensure the adequate quality of these products.[74] Nowadays, their use is limited to the intraoperative setting because of their long-term toxicity, and as a result they have been exchanged with SO (**Figure 3**) or another long-term vitreous substitutes.[75–77]

3.2.4. Semifluorinated Alkanes

Semifluorinated alkanes (SFAs) were identified in the 2000 s as an alternative to PFCLs given the presumption that the latter could cause retinal toxicity due to their high specific density. Moreover, SFAs maintain properties such as inertness, biocompatibility, interface tensions, etc., containing both perfluorocarbon and hydrocarbon segments. They have lower densities compared to PFCLs, ranging from 1.1 to 1.7 g cm^{-3}, and they are soluble in PFCLs, hydrocarbons and SO. They also have very low surface and interface tensions.[76]

The shorter the perfluoroalkyl chains and/or the longer the alkyl chain, the more toxic the semifluorinated alkanes are. Impurities containing –CHF groups must also be taken into account, given that hydrogen fluoride groups can be eliminated in the presence of nucleophilic bases, resulting in toxic alkenes.[76]

SFAs were initially used as SO solvent, and later as temporary endotamponades when it was observed that SO was ineffective.[78] The most common problems related to the use of SFAs are cataracts and emulsification. Nowadays, SFAs tend to be mixed with SO.

3.2.5. Silicon Oils and Semifluorinated Alkanes Combination

The combined use of SO and SFAs tamponade agents has been widely studied, with the idea of bringing together the high viscosity of SO and the high specific gravity of SFAs. This mixture generates vitreous substitutes that boast good tamponade properties and minimal emulsification.[79]

Depending on the proportion of SO and SFAs included in the mixture, it is possible to obtain homogeneous solutions (heavy silicone oils) or separated solutions (double fillings).[80]

Heavy silicone oils—Heavy silicone oils (HSO) are homogeneous solutions that are heavier than water and that are formed by combining SO and SFAs. In clinical practice, these are used for treating complicated RDs, especially those which involve inferior PVR. There are three prefabricated HSOs currently on the market: Densiron 68, Oxane HD, and HWS 46–3000.

Densiron 68 (Fluoron Co, Ulm, Germany) is a mixture of 30.5% SFA F_6H_8 (perfluorohexyloctane) with 69.5% SO, 5000 cSt.[78] By adding SO, the viscosity of F_6H_8 increases from 2.5 to almost 1400 mPa s, reducing its dispersion tendency, which is believed to cause the problems derived from the long-term use of F_6H_8. It has a specific gravity of 1.06 g cm^{-3} and a refractive index of 1.387.

Oxane HD (Bausch & Lomb, Toulouse, France) is a mixture of 88.1% Oxane 5700, a 5000 mPa s SO, with 11.9% RMN3, a partially fluorinated olefin. It has a slightly superior specific gravity and refractive index than water, 1.02 g cm^{-3} and 1.4, respectively. It is the most viscous, 3800 mPa s, and least heavy HSO of the three products. Because of its lower specific gravity, slightly higher re-detachment rates were found when using this HSO.[81]

The last commercialized HSO is called HWS 46–3000, which is a mixture of 45% ultrapurified SO 100 000 (viscosity 97 100 mPa s and specific gravity 0.977 g cm^{-3}) and 55% perfluorobutylhexane (F_4H_6) a semifluorinated alkane (viscosity 1.28 mPa s and specific gravity of 1.254 g cm^{-3}). The resulting solution (specific gravity of 1.105 g cm^{-3} and a viscosity of 3109 mPa s) is homogeneous and stable in the presence of water, air or PFCLs. It is the heaviest and most viscous mixture of the three. In the pilot study by Rizzo et al., high success and low complication rates were achieved when HWS 46–3000 was used as a long-term tamponade (1–3 months), even though, due to its higher viscosity, handling this substance may be more difficult, e.g., when removing it.[75]

Densiron 68, Oxane and HWS 46–3000 have shown promising results in the treatment of RDs associated with inferior tears.[82] However, in a prospective, multicentered, randomized controlled trial (HSO Study) that compared the effect of heavy tamponade (Densiron 68) and conventional SO in eyes with inferior and posterior PVR grade C or above, researchers concluded that there were no significant benefits to using heavy tamponade instead of conventional SOs in these cases.[29]

Double fillings—Double fillings are heterogeneous solutions in which the SFA sinks and the SO floats due to its specific gravity, meaning that they are able to provide superior and inferior tamponades simultaneously. The most commonly used SFA is perfluorohexyloctane (F_6H_8). The amount of F_6H_8 is much greater than the amount that can be dissolved by SO; therefore, the top part of the bubble consists of SO saturated with dissolved F_6H_8, whereas the bottom part of the bubble is pure F_6H_8. The most commonly reported combination is F_6H_8 mixed with 1000 cSt SO in a 3:7 proportion.[83,84] A combined internal tamponade of F_6H_8 and SO may be useful for treating complicated RD with breaks involving the retina's lower quadrants.[85]

In order to clarify all of the advantages and limitations of the vitreous substitutes that are currently used in clinical practice, these characteristics have been included in **Table 3**.

Table 3. Advantages and limitations of the vitreous substitutes used in clinical practice.

	Advantages	Limitations
Gases	- No need for removal - Non-toxic - Inert - Expansile	- Prone positioning after vitrectomy - Expansile gases can produce intraocular pressure elevation (IOP)
Silicone Oils	- Transparency - Low surface tension - Long-term internal tamponade - Low toxicity	- Must be removed within a 6-month period - Optical adjustments may be required - Less effective tamponade of the inferior retina due to its low specific gravity
Perfluorocarbon liquids	- Clear, colorless and odorless - Similar refractive index to vitreous humour - Stabilization of the retina during vitrectomy	- Limited to intraoperative setting - Long-term toxicity - Must be replaced with SO
Semifluorinated alkanes	- Less retinotoxicity than PFCLs due to its lower specific density - Soluble in PFCLs and SOs.	- Emulsification - Cataracts
Heavy Silicone Oils	- Good transparency, high density and viscosity - Good tamponade properties - Less tendency to disperse	- Difficult to handle due to its viscosity - Must be removed within a 2-month period.

4. Influence of Vitreous Substitution on Pharmacokinetics of Intravitreal Drugs

When the vitreous is substituted with SO, 80% of the vitreous cavity will be filled with the tamponade, while the rest will be replenished with aqueous humour and some vitreous remnants may be present. In the case of inert gas substitutes, the proportion that is to be refilled with the aqueous humour will increase as the gas disappears, and the time it takes to totally disappear will differ depending on the type of gas (Table 1). Artificial substitutes that are currently used in clinical practice differ in terms of their vitreous composition, and this may affect the pharmacokinetics of intravitreally injected drugs.[86] Most of these drugs are water-soluble and will only dissolve in the vitreous aqueous phase. To the best of our knowledge, very few intravitreal pharmacokinetic studies have been conducted on tamponade animal eye models[87,88] in

which SO was used as the vitreous substituent. In this sense, Xu et. al investigated the bevacizumab injection (1.25 mg/0.05 mL) in a rabbit model, observing that silicone acted as a temporary depot for controlled drug delivery, delaying drug distribution into the remaining vitreous aqueous phase, where the drug dissolved, before being further distributed into the surrounding tissues. Therefore, it is anticipated that the drug concentration-time profiles will change between the native and filled vitreous. However, given the lack of internal control the intravitreal clearance or half-life differences between SO-vitreous and the control healthy eye were not determined in those studies.[87,88] For ethical reasons it is not possible to perform these types of pharmacokinetic studies in patients. Nevertheless, a few studies have evaluated the safety and efficacy of treatment versus no-treatment in SO-filled eyes with antivirals[89] or bevacizumab injections,[90,91] observing positive clinical outcomes in the treated patients. Several other case reports have shown that the Ozurdex implant (dexamethasone 0.7 mg loaded in a biodegradable sustained-release intravitreal implant (Allergan Inc., Irvine, CA)) appears to be tolerated by and beneficial to patients with SO tamponade.[92–94] However, it must be noted that the reported clinical studies are based on a limited number of patients. The drug release from the implant will depend on the phase in which said implant is located, that is to say the aqueous phase or the SO/gas phase, as this release will only be possible in a medium in which the drug can be dissolved. In the case of acting-gas tamponade, the release may also be dependent on the timing of the gas disappearing. Moreover, the drug release from the implant may be delayed in the filled-eye, and longer drug levels may be maintained, nonetheless, further investigations on an animal models are required.[95]

Overall, there is still a lack of quantitative data on the effect of the vitreous substituents on intravitreal pharmacokinetics. Further pharmacokinetic studies must be conducted in order to clarify their effect on the drug concentrations following intravitreal administration, for both drug solutions and implants.

5. Experimental Vitreous Substitutes: Hydrogels

There are still numerous inconveniences and limitations to the use of currently available vitreous substitutes in clinical practice. Consequently, the search for new biomaterials that can be used to achieve the ideal vitreous substitute still continues. Previous research attempted to produce vitreous substitutes that boasted similar physiological properties and molecular structure to the vitreous body. The limits of this approach included the toxicity of the compounds and their incapacity to provide sufficient internal tamponade for vitreous replacement surgery.[96] In order to overcome these drawbacks, recent research has focused on developing biocompatible, biodegradable, and injectable hydrogels (natural, synthetic, and smart), which will also act as medium and long-term internal tamponade agents.[2] Hydrogels do not have to be removed after a certain period of time, therefore overcoming one of the main inconveniences related to this procedure. In addition, depending on the types of polymers used for their synthesis, some of their properties can be optimized. Specifically, their viscosity, porosity, good mechanical strength, and the possibility of drug encapsulation make these advantageous for their clinical use in patients. Main hydrogels which have been developed as vitreous substitutes in recent years have been outlined in **Table 4**.

5.1. Natural Hydrogels

The use of HA and collagen as vitreous substitutes has been evaluated due to their great biocompatibility and given that these are the main components of the vitreous. However, they have a poor tamponade effect and a limited retention time in vivo comparing to the results produced by synthetic and smart hydrogels, due to the molecules tendency towards degradation and their low viscosity.[23,97]

To increase retention time, HA has been cross-linked through UV and dihydrazide, resulting in biocompatible hydrogels that present good transparency, viscosity, and tamponade effect thanks to their hydrophilic properties, nonetheless, these materials still present relatively short-term stability.[99,103] In addition, cross-linked hyaluronate formulations and combinations of HA with other polymers, such as microbial anionic polysaccharide gellan have also been tested. However, due to the instability of the physical crosslinks, these combinations are not available for long-term use.[97,98,100,101]

Aiming to improve this feature, Raia et al. synthesized silk and HA composite hydrogels by cross-linking the tyrosine residues native to silk fibroin and tyramine-conjugated HA. In this sense, the composite silk-HA hydrogel retained the favorable properties of each of the polymers. Consequently, the better control of the water content in the composite matrix exerted by HA and the slow proteolytic degradation of the silk resulted in longer stability and durability.[125]

Additionally, Uesugi et al. used a natural polymer, which was not based on collagen or HA as a vitreous substitute. Specifically, they reported the use of PanaceaGel SPG-178 (0.1%), a self-assembling gel, the main component of which is 13 amino acid synthetic peptide. This gel can be injected through a 27-gauge needle and its refractive index, visible light transmission rate, and rheological properties are similar to those of human vitreous. In addition, they carried out a three-month in vivo study in rabbits in which good biocompatibility and no toxicity were observed.[102]

Nevertheless, rapid degradation remains a major problem for this type of substitutes, as biomaterials tend to degrade and change their physicomechanical properties in a short period of time. This is a considerable drawback given that the ideal vitreous substitutes must be stable for long periods of time, preferably over three months.[2,6]

5.2. Synthetic Hydrogels

Polymeric hydrogels are the next step towards producing the ideal vitreous substitute. These materials are networks of cross-linked hydrophilic polymer chains with extensive swelling, absorbing several times their own weight in water.[126,127] They have a good level of transparency, biocompatibility, and present viscoelastic properties that are similar to the vitreous body, imitating its biofunctionality.[128]

Poly(1-vinyl-2-pyrrolidone) (PVP) was the first synthetic polymer to be tested as a potential vitreous substitute. The most commonly reported adverse effects were vitreous opacification and inflammation reaction, resulting in early PVP degradation due to phagocytosis.[129] In addition, 1-vinyl-2-pyrrolidone (VP) monomer was polymerized with divinyl glycol (DVG) as a

Table 4. Hydrogels developed as vitreous substitutes and their main characteristics.

Hydrogels	Polymer content [%]	Refractive index	Light transmittance [%]	In vivo studies	Reference
Natural polymers					
Gellan and hyaluronic acid	1		85–95	no	[97]
Methacrylated gellan gum	1			no	[98]
Hyaluronic acid	1	1.338		rabbits	[99]
Hyaluronic acid	3	1.341		rabbits	[100]
Hyaluronic acid	1–2.2	1.32–1.34		rabbits	[101]
Peptide gel	0.10	1.3339	96.7	rabbits	[102]
Hyaluronic acid	1	1.32–1.33		rabbits	[103]
Hyaluronic acid	1	1.336	75–91	no	[23]
Synthetic polymers					
Polyvinyl alcohol methacrylate	9			no	[104]
Polyvinyl alcohol	7			macaques	[105]
Polyvinyl alcohol	4		85	no	[106]
Poly(ethylene glycol)	5	1.339		rabbits	[107]
Polyvinyl alcohol	5			no	[108]
Polyvinyl alcohol	1–7	1.3361	93	rabbits	[109]
Polyvinyl alcohol	4	1.3420		no	[110]
Acrylic acid and acrylamide	1.25 –1.75			no	[111]
Poly *N*-acryloyl glycinamide-polycarboxybetaine acrylamide	1.60	1.3354	93.2	rabbits	[112]
Smart hydrogels					
WTG-127			89.3	rabbits	[113]
Poly(ethylene glycol)	25	1.353	>90	no	[114]
Poly(ethylene glycol)	10	1.3325		rabbits	[115]
Sulfobetaine methacrylamide and acryloyl cystamine monomers	5		>90	rabbits	[116]
Gellan and poly(methacrylamide-*co*-methacrylate)	0.65–1.29	1.3351–1.3372	87.6–94	rabbits	[117]
Methacrylic acid, methylacrylamide, and bismethacryloylcystamine	1–1.4			no	[118]
Poly(ethylene glycol)	0.4–0.7			rabbits	[119]
Polymethacrylamide and poly-methacrylate	0.9–1.8	1.3345–1.3348	>95	no	[120]
Hydroxypropyl chitosan and alginate dialdehyde	1–3	1.3348	>80	rabbits	[121]
Poly(ethylene glycol), poly(propylene glycol), and poly(ϵ-caprolactone)	3–12	1.339–1.344		rabbits	[122]
Poly(ethylene glycol) methacrylate and poly(ethylene glycol) diacrylate	0.75–5.7	1.3350–1.3359	>90	no	[123]
Gellan and poly(methacrylamide-*co*-methacrylate-*co*-bis(methacryloyl)cystamine)		1.3355–1.3370	>83	rabbits	[124]

cross-linking agent in order to obtain a transparent hydrogel with a similar density and viscosity to the vitreous body.[129] Finally, VP was also co-polymerized with 2-hydroxyethyl methacrylate (HEMA) using diallyl ether (DAE) as a cross-linking agent, resulting in a clear and transparent gel with mechanical properties close to those of the vitreous, however, the main inconvenience was that the elastic properties were reduced or even lost when injected.[130]

Polyacrylamide (PAA) has been synthesized by the polymerization of acrylamide, a toxic and carcinogenic substance, with a disulfide cross-linking agent. However, this polymerization process highly improves its biocompatibility. PAA presents good biocompatibility and long-term stability, as well as offering a similar viscosity and density to the vitreous. With regards to adverse reactions, severe ocular inflammation and vitreous opacification have been reported.[131]

Poly(2-hydroxyethylacrylate) (PHEA) presented very good physical properties; however, due to the emergence of inflammatory reactions, as well as cataract and glaucoma this substance is no longer being investigated.[4,6]

All of the aforementioned polymers presented complications related to inflammation and toxicity. As a result, other polymers such as poly(glyceryl methacrylate) (PGMA) and hydroxypropyl methylcellulose (HPMC) were investigated; however, these did not reach the clinical study stage due to their short degradation time.[132,133]

In recent years, further polymer-based hydrogels, which are presented below, have been synthesized in order to overcome some of the previously mentioned drawbacks.

Poly(vinyl alcohol) (PVA) presents good biocompatibility, as well as optical and rheological properties. In addition, it cannot be differentiated from the natural vitreous during the first months after the injection. All these features make it an optimum vitreous substitute and its rheological characteristics and diffusion behavior can be further improved by adding trisodium-triphosphate as a cross-linking agent. However, there is still insufficient data regarding its tamponade properties.[105,106,108–110]

Poly(vinyl alcohol methacrylate) (PVA-MA) is more hydrophobic than PVA due to its increased metacrylate content; however, the polymer's backbone is hydrophilic enough to form a hydrogel. The inclusion of a photoinitiator, which forms a gel network after irradiation at 365 nm is a unique characteristic of this gel. The degree of gelification can be regulated by light intensity and polymer concentration. Nevertheless, more studies are necessary in order to evaluate the vitreous biocompatibility of PVA-MA.[104]

Copolymers of PAA (CPA) are derived from PAA; however, these acquire better gelification properties, through polymerization after a reduction of the disulfide cross-linking bridges. These polymers have similar viscoelastic properties and refractive index to the vitreous, as well as good compatibility and a lack of significant ocular toxicity, positioning itself as a good alternative for long-term substitution.[131]

Poly(2-hydroxylethyl methacrylate) (pHEMA) presents solid properties, meaning that its implantation proves difficult. Its administration through a small hole during the vitreo-retinal surgical procedure is not possible, requiring a surgical incision, which makes the surgery more complex as well as producing greater trauma to the eye.[134,135]

Poly(ethylene glycol) (PEG) in aqueous solution at 5 wt% was tested in an in vivo rabbit model. It boasted optical and physical characteristics similar to natural vitreous and was well tolerated. However, the solution was not retained throughout the postoperative period, meaning that the residence time would have to be increased through polymer cross-linking.[107]

Beta cyclodextrin polymeric interacts with hydrophobic poly {(2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt)-co-[6-(acrylamido)-*N*-adamantylhexaneamide]} when mixed in water to create a hydrogel. Bhöm et al. synthesized this gel and tested it in vitro as a vitreous substitute which presented biocompatibility. However, the authors concluded that it was necessary to reconsider the use of this hydrogel due to the cytotoxic effects caused by the adamantyl-functionalized polymer.[136]

Davis et al. used acrylic acid in combination with acrylamide in order to synthesize a hydrogel with bis-acryloylcystamine as a reversible cross-linker. The formulation was tested in vitro, and it remained optically clear, presenting biocompatibility. However, it caused an inflammatory response in the retinal cells.[111]

Poly *N*-acryloyl glycinamide-poly carboxy betaine acrylamide is a supramolecular binary hydrogel which is formed by copolymerization of its two components, which are physically cross-linked by dual amide hydrogen bonds, presenting an ultralow solid content. Wang et al. demonstrated that it was biocompatible and that its light transmittance and refractive index were very close to those of the vitreous. In addition, they observed that this hydrogel could be injected into the rabbits' eyes using a 22G needle, with rapid recovery of the gelling network. After a 16-week in vivo study, the hydrogel remained very stable, without affecting any structure in the eye or producing adverse effects. Consequently, after the necessary clinical trials have been conducted, this hydrogel could be considered as an interesting alternative for long-term vitreous substitution.[112]

5.3. Smart Hydrogels

Polymer-based hydrogels emerged as a promising alternative for vitreous substitution. However, the mechanical properties of most of these is modified during the injection process when they are pushed through a small-gauge needle.[124] The shear degradation causes the rupture of polymeric chains, resulting in loss of elasticity and fluidification.[137]

As a result, smart hydrogels may constitute a potential alternative due to the fact that they can be prepared, stored and injected as a solution and gelate in situ, via external stimuli.[138] These hydrogels are held together by noncovalent interactions such as electrostatics, hydrogen bonding, and hydrophobic forces.[139] They can effectively dissipate mechanical energy due to their inherent reversibility and dynamism, which allows sol-to-gel transitions. These reversible transitions facilitate the injection procedure as well as the possible future removal.[2,140]

In this way, Tao et al. developed an in situ chemically cross-linked hydrogel system, which consisted of two components, both based on multifunctional PEG but with complementarily reactive end groups of thiol and active vinyl groups. The system, when injected reacts via the Michael addition route and forms a chemically cross-linked hydrogel in situ. It was tested in vivo in rabbits, remaining transparent and stable for a 9-month period, with no adverse effects. Therefore meaning that after successful clinical trials have been conducted this hydrogel could be suitable as a potential long-term vitreous substitute.[115]

Similarly, Chang et al. synthesized a zwitterionic polymer poly(MPDSA-*co*-AC) as a copolymer of the sulfobetaine methacrylamide and acryloyl cystamine monomers, providing the zwitterionic components and the thiol functional groups, respectively. The in situ gelation was also via the Michael addition route with PEGMA as the cross-linker. In vivo studies in rabbits showed optimum transparency and biocompatibility but only for a 2-month period.[116] Consequently, further studies will be required in order to evaluate its potential use as long-term substitute.

Continuing with in situ hydrogels, Hayashi et al. developed an oligo-Tetra-PEG hydrogel, by mixing tetra-armed poly(ethylene glycol) with thiol termini (Tetra-PEG-SH) and maleimide termini (Tetra-PEG-MA) as a long-term vitreous substitute. The authors demonstrated that this hydrogel was effective in the treatment of RD in rabbits' eyes for a period of one year without any adverse effects. These results suggest that this could be used as a long-term vitreous substitute once the necessary clinical trials have been conducted.[119]

In this regard, Liang et al. combined polymethacrylamide (PMAM) with the anionic nature of polymethacrylate (PMAA) to make copolymers by using bis-methacryloyl cystamine (BMAC),

introducing thiol groups for reversible crosslink. They stated that copolymers with higher MAA content gelled faster, swelled more, and had higher storage modulus compared to that of natural vitreous. The authors confirmed the biocompatibility in vitro; however, they did not provide any information on the in vivo evaluation.[141]

For their part, Jiang et al. developed a hydrogel of hydroxypropyl chitosan with alginate dialdehyde by crosslinking with BMAC to introduce thiol groups for reversible crosslink. When injected through a double-syringe injector with a Y-joint, the substance formed an in situ gel in 1–3 min. It presented optimum physical characteristics and rheological properties similar to those of the vitreous and it proved biocompatible in vitro. However a 90-d in vivo rabbit study showed both a decrease in the number of cones and rods in the rabbits' eyes and a decline in vision.[121]

Thermoresponsive hydrogels can be easily applied in clinical practice as they can be injected in liquid form, at room temperature, and undergo gelation in situ at physiological temperature when administrated.[142] In this sense, it is necessary to mention the studies carried out with Pluronic-127 and WTG-127.[113,143] Pluronic-127 boasts promising physical properties, showing a thermoreversible gelation behavior at concentrations of 20 wt% and above, assuming liquid form when cold but forming a clear gel at 21 °C.[144] Nevertheless, it was found to be unsuitable for vitreous substitution due to the induction of severe retinal toxicity.[143] On the other hand, WTG-127 was associated with low stability and diffusion under the retina before gelation was complete.[113]

In this sense, Annaka et al. developed a thermosensitive hydrogel based on PEG end-capped with an octadecyl groups (E10KDC18). This hydrogel was tested in vitro and in vivo, showing the optimum requirements for clinical use: clarity and transparency, biological and chemical inertness, nonabsorbable and nonbiodegradable characteristics, refractive index similar to natural vitreous, sufficient rigidity to act as tamponade agent, and ability to be injected through small-gauge needles. However, further studies must be carried out in order to evaluate its long-term biocompatibility.[114]

Continuing on with the idea of using thermoresponsive hydrogels as vitreous substitutes, some authors have synthesized a biomimetic hydrogel composed of thiolated gellan as an analogue of type II collagen and poly(methacrylamide-*co*-methacrylate-*co*-bis(methacryloyl)cystamine), a polyelectrolyte, as an analogue of hyaluronic acid.[117,118,124] This thermosensitive hydrogel can be injected as a viscous solution at 45 °C. Once in the eye, this substance forms a physical gel in situ when it reaches body temperature. The biocompatibility was tested in vitro, and, likewise, in vivo studies were performed on rabbits, with satisfactory results achieved in both cases with transparent corneas, and neither inflammation in the anterior segment, nor cataract development. However, further studies are required in order to demonstrate that it is a superior alternative to the materials that are currently being used.[124]

The ideal smart hydrogel has not yet been created and in order for the optimum smart hydrogel to be achieved, which satisfies all of the required criteria, not only in preclinical studies, but also in the adequately designed clinical trials, further studies will be required.

5.4. Future Prospects in Vitreous Substitution

Hydrogels used as vitreous substitutes could also act as vehicles to perform the slow and controlled release of certain drugs if needed. In this sense, Tram et al. have synthesized vitreous substitute hydrogels composed of poly(ethylene glycol) methacrylate (PEGMA) and poly(ethylene glycol) diacrylate (PEGDA), which underwent in vitro and in vivo testing. These hydrogels deliver vitamin C in order to protect ocular tissues, specifically the lens, from oxidative stress and cataract formation after vitreous humor removal, with the potential to reduce the cost of additional surgeries currently required for patients.[123] However, further studies are needed to evaluate the clinical efficacy of this type of hydrogel in reducing oxidative stress and cataract formation in clinical practice.

Liu et al. made important progress in the field of vitreous substitution. These authors synthesized a tricomponent multiblock thermogelling polymer, which consists of hydrophilic PEG, poly(propylene glycol) (PPG) and poly(ϵ-caprolactone) (PCL) segments linked together via urethane bonds. They demonstrated long-term biocompatibility in rabbit vitrectomy and nonhuman primate retinal detachment models. This hydrogel biodegrades in the months after surgery and, likewise, it promotes the reformation of a vitreous-like body that imitates the biophysical properties of the natural vitreous. Furthermore, it may constitute a very interesting alternative for long-term vitreous substitution.[122]

With regards to intravitreal administrations, it has been reported that certain syringes may release silicone droplets, which are interiorly recovered by certain kinds of silicones, causing vision impairment and sterile endophthalmitis. In this regard, in recent times the regulatory agencies have published warnings and as a consequence, further studies must be conducted to develop new lubricant materials which do not cause these adverse consequences.[145–147]

In the future, greater efforts must be made regarding the development of regeneration-eliciting artificial vitreous that can act as postsurgery tamponade agents, enhancing the total regeneration of a vitreous-like body, with improved versatility and efficiency.[148]

6. Conclusions

Vitreous substitution is indicated in the treatment of several vitreo-retinal disorders. At present, there are a wide range of vitreous substitutes available for use in clinical practice (gases and liquids); however, despite boasting certain advantages, there are also several inconveniencies in their use, which has meant that they are not the ideal substances for this purpose. In recent years, research has focused on the development of hydrogels based on different types of biomaterials. Specifically, considerable advances have been made in the development of smart hydrogels, with these representing the most promising alternative for vitreous substitution due to the numerous advantages that are offered by their reversible transition solution-gel. Despite the fact that many biomaterials have been synthesized, to date, no hydrogel has arrived to the clinical stage. Consequently, further studies must be carried out in the area in order to find the ideal vitreous substitute and introduce it into clinical practice.

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Conflict of Interest

The authors declare no conflict of interest.

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